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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
DUNSTON, JENNIFER ANN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/767,630	EHMANN ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 5/27/2005, in which claims 1, 3, 5-9 and 11-20 were canceled; and claims 2, 4 and 10 were amended. Claims 2, 4 and 10 are currently pending and under consideration.

Any rejection of record in the previous office actions not addressed herein is withdrawn. New grounds of rejection are presented herein that were not necessitated by applicant's amendment of the claims since the office action mailed 1/25/2005. Therefore, this action is not final.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for plating a confluent monolayer of non-proliferating LA7 cells and human bladder epithelial cells in medium on culture support, wherein the LA7 cells form tight junctions with the human bladder epithelial cells, does not reasonably provide enablement for the formation of tight junctions between any non-proliferating epithelial cells and human bladder epithelial cells. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. **This is a new rejection.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claim, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claim, with the most relevant factors discussed below.

Nature of the invention: The claim is drawn to a method of culturing human bladder epithelial cells, comprising plating a confluent monolayer of non-proliferating epithelial cells and human bladder epithelial cells in medium on a culture support, wherein the non-proliferating cells are cells with which the human epithelial cells form tight junctions.

The nature of the invention is complex in that the appropriate cell-cell contacts must be made between the two cell types for a tight junction to form. Dorland's Illustrated Medical Dictionary defines the term "tight junction" as an intercellular junction at which adjacent plasma membranes are joined tightly together, separated by only 1 to 2 nm; these junctions variably occlude the intercellular space and limit or eliminate the intercellular passage of molecules.

Breadth of the claims: The claims are broad in that any epithelial cell from any source may be used as the non-proliferating epithelial cell with which the tight junctions must form. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification broadly envisions the use of feeder cells selected from established cell lines of human or animal

cell lines, such as LA7 rat mammary cells or other epithelial cells with which the cultured epithelial cells form cell-cell interactions (e.g. paragraph [0056]). The specification teaches that "it is likely that the success of this method depends on stimulation by membrane bound growth factors and/or the formation of physical junctions between the feeder cells and the epithelial cells" (see paragraph [0077]). Further, the specification teaches that the membrane-bound growth factors and physical junctions necessary for proliferation stimulation may be similar in some different tissues and in some tissues of different species (e.g. paragraph [0078]). However, the specification does not provide guidance with regard to the identity of the membrane-bound growth factors required for the method.

The working examples teach the culture of bladder cells from bladder washes and from human bladder specimens on lethally irradiated LA7 cells (e.g. Example 1). The working examples demonstrate that only bladder cells in direct contact with the LA7 cells proliferated (e.g. paragraphs [0096]-[0097]). Further, the working examples demonstrate that tight junctions form between the bladder epithelial cells and LA7 cells by incubating the cells with an antiserum to the ZO1 protein of tight junctions (e.g. paragraph [0100]-[0101]; Figure 6).

Although the specification envisions the use of other non-proliferating cells other than LA7 cells, the specification does not teach any other specific examples of cells lines that are capable of forming tight junctions with the epithelial cells.

Predictability and state of the art: The state of the art with regard to determining which epithelial cells will be capable of forming tight junctions in culture was underdeveloped and unpredictable at the time the invention was made. Taylor-Papadimitriou et al (Int J Cancer. Vol. 20, No. 6, pages 903-908, 1977, cited in a prior action) teach the co-culture of mammary

epithelium with non-proliferating lens epithelium (e.g. Abstract; page 903, *Fractionation and freezing down of milk cells, Recovery and culture of milk epithelial cells*). Further, Taylor-Papadimitiou et al teach that the mammary epithelial cell colonies will only form on the surface of the tissue culture dish without the lens epithelial cells (e.g. Figure 5). Thus, the cells are not capable of growing in close contact and cannot form tight junctions. Barsky et al teach the culture of carcinoma cells on myoepithelial feeder layers (see the rejection under 35 U.S.C. 103 below). However, the feeder layer was unable to form interepithelial junctions such as tight junctions (e.g. column 20, lines 44-47). Thus, at the time the invention was made, one was aware of the unpredictable nature of epithelial cell-cell contacts in culture.

Around the time the invention was made, numerous proteins that participate in the formation of tight junctions were known, including some "signaling" proteins involved in junction assembly (Anderson, News Physiol Sci, Vol. 16, pages 126-130, 2001; e.g. paragraph bridging pages 127-128). Further, Anderson teaches that there is a possibility that additional proteins that control paracellular permeability remain to be discovered (e.g. page 129, right column, last paragraph).

Amount of experimentation necessary: The quantity of experimentation necessary to make and use the claimed invention is high, as the skilled artisan could not rely on the prior art or specification to teach how to make and use any non-proliferating epithelial cell capable of forming tight junctions with a bladder epithelial cell. The specification does not teach the cell surface molecules necessary for the formation of tight junctions between the non-proliferating epithelial cells and the bladder epithelial cells. Thus, one would have to perform a large amount of trial and error experimentation to identify epithelial cell types capable of forming tight

junctions with bladder epithelial cells in culture. One may have to identify proteins involved in the process of forming tight junctions in order to identify cells capable of forming tight junctions or to confer the ability of tight junction formation through heterologous expression of the protein in a cell that is not capable of forming a tight junction in culture.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claim 4 is not considered to be fully enabled by the instant specification.

Claim Rejections - 35 USC § 103

Claims 1 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barsky et al (US Patent No. 5,643,787, cited in a prior action; see the entire reference) in view of Crook et al (BJU International, Vol. 86, pages 886-893, 2000; see the entire reference). **This is a new rejection.**

Barsky et al teach a method of culturing epithelial cells on a feeder layer of myoepithelial cells (e.g. the cell lines HMS-1 and HMS-X), comprising placing the epithelial cells onto the feeder layer and incubating the cultures to allow active mitogenesis (e.g. column 3, lines 51-67; column 4, lines 51-67). Further, Barsky et al teach a cell culture produced by the method (e.g. column 3, lines 51-67; column 4, lines 51-67). Barsky et al teach irradiation of the feeder layer to prevent further cell division, without killing the cells (e.g. column 4, lines 46-50). Epithelial cells taught by Barsky et al include HMS-1 myoepithelial cells, HMS-3 salivary gland epidermoid carcinoma cells, MCF-7, MDA-MB-231 breast adenocarcinoma cells, 10 primary

prostate carcinoma cultures, 10 primary breast carcinoma cell cultures, and 5 breast carcinoma in situ cultures (e.g. column 19, lines 1-21). Feeder layer cells taught by Barsky et al include HMS-1 and MCF-7 breast carcinoma cells (e.g. column 19, lines 1-21). Dorland's Illustrated Medical Dictionary defines carcinoma as a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Further, ATCC defines MCF-7 cells as human mammary epithelial cells. Therefore, the feeder cells taught by Barsky et al are non-proliferating epithelial cells upon which human epithelial cells of a luminal organ are grown. Moreover, Barsky et al teaches the use of the culture to investigate the mechanisms of cell attachment and tumor invasion and metastases (e.g. column 10, lines 20-54).

Barsky et al do not teach the growth of bladder epithelial cells such as bladder carcinoma cells on the non-proliferating epithelial cells.

Crook et al teach a bladder cancer cell line transfected with GFP using the GFP vector pEGFP-N1 (e.g. page 887, paragraph bridging columns). Crook et al teach that in the past carcinoma cells have been observed by conventional histology or by SEM, whereas the GFP transfected bladder carcinoma cells allow living tumor colonies to be viewed without terminating the experiment (e.g. page 890, paragraph bridging columns).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the GFP transfected bladder carcinoma cell line of Crook et al in the cell culture system of Barsky et al because Barsky et al and Crook et al teach it is within the skill of the art to culture carcinoma cells *in vitro*.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to visualize the tumor cells in assays for cell attachment, tumor

invasion and formation of metastases without having to kill the cells as taught by Crook et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jennifer Dunston
Examiner
Art Unit 1636

jad

TERRY MCKELVEY
PRIMARY EXAMINER